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[Intervention Review]

Opioids for restless legs syndrome

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ABSTRACT

Background

Restless legs syndrome (RLS) is a distressing and common neurological disorder that may have a huge impact in the quality of life of those with frequent and intense symptoms. Patients complain of unpleasant sensations in the legs, at or before bedtime, and feel an urge to move the legs, which improves with movement, such as walking. Symptoms start with the patient at rest (e.g. sitting or lying down), and follow a circadian pattern, increasing during the evening or at night. Many pharmacological intervention are available for RLS, including drugs used to treat Parkinson's disease (L-Dopa and dopaminergic agonists), epilepsy (anticonvulsants), anxiety (benzodiazepines), and pain (opioids). Dopaminergic drugs are those most frequently used for treatment of RLS, but some patients do not respond effectively and require other medication. Opioids, a class of medications used to treat severe pain, seem to be effective in treating RLS symptoms, and are recommended for patients with severe symptoms, because RLS and pain appear to share the same mechanism in the central nervous system. All available drugs are associated to some degree with side effects, which can impede treatment. Opioids are associated with adverse events such as constipation, tolerance, and dependence. This justifies the conduct of a systematic review to ascertain whether opioids are safe and effective for treatment of RLS.

Objectives

To asses the effects of opioids compared to placebo treatment for restless legs syndrome in adults.

Search methods

We searched the Cochrane Central Register of Controlled trials, CENTRAL 2016, issue 4 and MEDLINE, EMBASE, and LILACS up to April 2016, using a search strategy adapted by Cochraneto identify randomised clinical trials. We checked the references of each study and established personal communication with other authors to identify any additional studies. We considered publications in all languages.

Selection criteria

Randomised controlled clinical trials of opioid treatment in adults with idiopathic RLS.

Data collection and analysis

Two review authors independently screened articles, independently extracted data into a standard form, and assessed for risk of bias. If necessary, they discussed discrepancies with a third researcher to resolve any doubts.

Main results

We included one randomised clinical trial (N = 304 randomised; 204 completed; 276 analysed) that evaluated opioids (prolonged release oxycodone/naloxone) versus placebo. After 12 weeks, RSL symptoms had improved more in the drug group than in the placebo group

(using the IRLSSS: MD -7.0; 95% CI -9.69 to -4.31 and the CGI: MD -1.11; 95% CI -1.49 to -0.73). More patients in the drug group than in the placebo group were drug responders (using the IRLSSS: RR 1.82; 95% CI 1.37 to 2.42 and the CGI: RR1.92; 95% ICI 1.49 to 2.48). The proportion of remitters was greater in the drug group than in the placebo group (using the IRLSSS: RR 2.14; 95% CI 1.45 to 3.16). Quality of life scores also improved more in the drug group than in the placebo group (MD -0.73; 95% CI -1.1 to -0.36). Quality of sleep was improved more in the drug group measured by sleep adequacy (MD -0.74; 95% CI -1.15 to -0.33), and sleep quantity (MD 0.89; 95% CI 0.52 to 1.26).

There was no difference between groups for daytime somnolence, trouble staying awake during the day, or naps during the day. More adverse events were reported in the drug group (RR 1.22; 95% CI 1.07 to 1.39). The major adverse events were gastrointestinal problems, fatigue, and headache.

Authors' conclusions

Opioids seem to be effective for treating RLS symptoms, but there are no definitive data regarding the important problem of safety. This conclusion is based on only one study with a high dropout rate (low quality evidence).

PLAIN LANGUAGE SUMMARY

Opiods for restless legs syndrome

Background

Restless legs syndrome (RLS) is a very common neurological disorder in which patients complain of an intense need to move their legs, and unpleasant sensations felt deep in their legs, all occurring while at rest, mostly at bedtime. The number of patients complaining of RLS varies according to race, gender, age, country, and health status. About 5% to 10% of people are affected; , and, among these, 2% to 5% need continual pharmacological treatment (medication). When RLS does not respond to medications generally used for Parkinsons Disease and epilepsy, their doctors often prescribe opioids.

Question

Are opioids effective and safe for people with RLS?

Methods

We searched the literature for studies in any language, published or not, that considered opioids for the treatment of RLS

Results

We included one randomised controlled clinical trial with moderate risk of bias that tested a combination of oxycodone and naloxone against placebo capsules, taken twice daily in participants whodid not respond to more usual medications. Researchers used the International RLS severity scale to find out if patients were improved after 12 weeks of treatment. Particpants receiving the combined oxycodone and naloxone reported improvement in RLS symptoms, Quality of life, and sleep quality; 42% of the drug group were symptom-free.

Discussion

The study was well designed overall, but was at a high risk of bias due to the high percentage of participants who withdrew from treatment (attrition bias). Eighty-four percent of the drug group developed adverse events, which were mostly related to the gastrointestinal system, headache, fatigue, and sleepiness (somnolence); 9.8% left the study because of the adverse events.

Conclusion

The use of opioids for the treatment of RLS in patients resistant to conventional treatment is supported by low-quality evidence. Prescription of these medications should be based on clinical experience, and caution used due to the potential for abuse, dependency, and adverse events. No patient on opioids complained that their symptoms worsened.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Opioids compared to placebo for RLS

Opioid treatment compared to placebo for patients with RLS

Patient or population: RLS
Setting: 55 hospitals and specialised private neurology practices in Austria, Germany, Spain, and Sweden.
Intervention: opioids
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with opioids				
RLS symptoms assessed with: IRLSSS Scale from: 0 to 40 follow up: mean 12 weeks	The mean RLS symptoms was 22.1 points	The mean RLS symptoms in the intervention group was 7 points lower (9,69 lower to 4,31 lower)	-	270 (1 RCT)	⊕⊕⊖⊖ LOW [1]	Moderate effect size of difference in mean response (0.57) [2]
RLS symptoms assessed with: CGI Scale from: 0 to 7 follow up: mean 12 weeks	The mean RLS symptoms was 4.1 points	The mean RLS symptoms in the intervention group was 1,11 points lower (1,49 lower to 0,73 lower)	-	276 (1 RCT)	⊕⊕⊖⊖ LOW [1]	Moderate effect size of difference in mean response (0.64) [2]
Drug responders assessed with: IRLSSS - Reduced score at least 50% follow up: mean 12 days	Study population		RR 1.82 (1.37 to 2.42)	276 (1 RCT)	⊕⊕⊖⊖ LOW [1]	
	313 per 1.000	569 per 1.000 (428 to 756)				
Drug responders assessed with: CGI - Self reported "Much improved" or "Very much improved" follow up: mean 12 weeks	Study population		RR 1.92 (1.49 to 2.48)	276 (1 RCT)	⊕⊕⊖⊖ LOW [1]	
	347 per 1.000	667 per 1.000 (517 to 861)				
Remitters assessed with: IRLSSS - Scored 10 or less follow up: mean 12 weeks	Study population		RR 2.14 (1.45 to 3.16)	276 (1 RCT)	⊕⊕⊖⊖ LOW [1]	
	194 per 1.000	416 per 1.000 (282 to 614)				

Adverse Events assessed with: clinical assessment follow up: mean 12 weeks	Study population		RR 1.22 (1.07 to 1.39)	304 (1 RCT)	⊕⊕⊝⊝ LOW [1]	
	688 per 1.000	840 per 1.000 (736 to 957)				
Quality of life assessed with: RLS Quality of Life Questionnaire (RLS-QoL) Scale from: 0 to 7 follow up: mean 12 weeks	The mean quality of life was 3.64 points	The mean quality of life in the intervention group was 0,73 points lower (1,1 lower to 0,36 lower)	-	276 (1 RCT)	⊕⊕⊝⊝ LOW [1]	Small effect size of difference in mean response (0.43) [2]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] The only trial included presentes high risk of attrition bias.
[2] 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect of difference in mean response (Cohen 1988).

BACKGROUND

Description of the condition

Restless legs syndrome (RLS) is a sensorimotor disorder characterised by a distressing urge to move the legs, and sometimes, other parts of the body as well, usually accompanied by a marked sense of discomfort or pain in the leg or other affected body parts (Allen 2003).

The prevalence of RLS is estimated at 5% to 15% in adults. It is more common in women, and can affect children as well (Picchietti 2005; Picchietti 2007[Yeh 2012). When frequency, severity, or a combination of symptoms is added to the diagnostic criteria, the prevalence of RLS ranges from 2.2% to 7.9%. If the diagnosis is based on a clinical interview, taking into account all possible differential diagnoses, the prevalence declines to between 1.9% and 4.6% (Ohayon 2012).

Other features commonly found in adults with RLS include sleep disturbance, daytime fatigue, and decreased quality of life ratings, mostly in patients who also have iron deficiency anaemia (Allen 2013; Picchietti 2005).

The physical examination is typically normal. restless leg syndrome may be either idiopathic (primary RLS, which often has a familial component) or secondary, occurring in conjunction with other medical conditions, particularly iron deficiency anaemia, pregnancy, or end-stage renal disease. Secondary RLS tends to remit without evidence of reoccurrence when the secondary condition is resolved, for example, after renal transplantation in patients with end-stage renal disease, and postpartum in women with RLS during pregnancy (Lee 2001; Winkelmann 2002).

Periodic leg movements in sleep (PLMS) are characterized by brief (0.5- to 5.0-second) lower-extremity movements during sleep, which typically occur at 20- to 90-second intervals, most commonly during the first three hours of sleep. The affected individual is usually not aware of the movements or of the associated transient partial arousals (Picchietti 2005; Trenkwalder 2005). Overall, 80% to 90% of individuals with RLS have PLMS, but PLMS are not necessarily associated with RLS (Hornyak 2006; Rye 2012). The prevalence of PLMS in the general population is 3.9% (Ohayon 2002).

Description of the intervention

The treatment of RLS includes pharmacological and non-pharmacological therapies. The most common pharmacological agents used in clinical practice are levodopa, dopamine agonists, opioids, benzodiazepines, and anticonvulsants (Garcia-Borreguero 2013; Trenkwalder 2005).

The precise mechanisms by which opiates ameliorate RLS are not well understood. Opiate receptors have been identified in the dorsal horn, where they are believed to participate in the regulation of incoming nociceptive sensory information. Opiates are also highly concentrated in brainstem areas, around the periaqueductal grey and in the basal ganglia (striatum, substantia nigra); each of these areas could be sites in which the opioids act to improve symptoms of RLS (Sandyk 1987). Involvement of the dopamine system in RLS pathophysiology seems probable, but involvement of the opiate system is less clear.

Narcotic medications generally have a relatively low potential for addiction, and cause little tolerance in the RLS population (Winkelmann 2002). Side effects include nausea, sedation, dizziness, and constipation. There are still concerns about the potential for abuse, addiction, and practical problems, so the treatment of RLS with opioids remains controversial.

The essentially normal presynaptic dopaminergic binding studies using F-dopa PET or B-CIT-SPECT (diagnostic imaging tools) in patients with RLS lend support to the hypothesis that dopaminergic neurons and spinal pathways could be involved more in the pathophysiological mechanisms of the syndrome than the nigrostriatal system (Wetter 2004).

Althoug dopamine can be increased in the synaptic cleft of patients with RLS, the strongest evidence for a dopaminergic role in the pathophysiology of RLS comes from the pharmacological response to medications that increases dopamine function (Allen 2004; Earley 2013). Functional imaging studies have shown reduced fluoro dopa uptake or reduced D2 receptor binding in the corpus striatum (Wetter 2004).

Iron is a cofactor in dopamine production, and RLS patients exhibit a deficiency of iron in the brain. Studies with iron-deprived rats indicate that low CSF ferritin and high transferrin can be expected to occur with reduced brain iron (Allen 2004; Rizzo 2013).

How the intervention might work

The endogenous opioid system plays a role in pain transmission , and there is evidence of opioid receptors involvement in the pathogenesis of RLS (Hening 1986; Mizoguchi 2014). A post-mortem study of the brains of patients with RLS showed deficiencies of beta-enkephalin and met-endorphin in the thalamus (Walters 2009), which also suggests a direct implication of this system in the pathogenesis of RLS symptoms. Furthermore, mu-receptors in rats presented signs suggestive of RLS, and interestingly, iron deficiency, which is somehow related to the clinical picture of RLS (DeAndrade 2013; Earley 2014). Hence, there is a body of data supporting the hypothesis that opioid drugs can improve endogenous opioid system function, thus providing improvement or even complete relief of RLS symptoms.

Why it is important to do this review

Many pharmacological intervention are available for RLS, including drugs used to treat Parkinson's disease (L-Dopa, dopaminergic agonists), epilepsy (anticonvulsants), anxiety (benzodiazepines), and pain (opioids). Dopaminergic drugs are the most frequent treatment used for RLS, but some patients do not respond effectively and require other medication. Opioids, a class of medications used to treat severe pain, seem to be effective in treating RLS symptoms and are recommended for patients with severe symptoms, because RLS and pain appear to share the same mechanism in the central nervous system. All available drugs are associated to some degree with side effects, which can impede treatment. Dopaminergic drugs can cause worsening of symptoms, which is known as augmentation, anticonvulsant drugs are associated with somnolence, and benzodiazepines are beneficial only for minor symptoms of RLS. Opioids are associated with adverse events such as constipation, tolerance, and dependence. This justifies the conduct of a systematic review to

ascertain whether opioids are safe and effective for the treatment of RLS.

OBJECTIVES

To evaluate the efficacy and safety of opioid treatment for idiopathic RLS.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (defined as trials using inadequate allocation assignment such as date of birth, day of the week or month of the year, person's medical record number, or simply allocating every alternate person). We considered studies with a parallel or a cross-over design.

Types of participants

Inclusion criteria

We considered children and adults who met any clinical criteria for idiopathic RLS (ICSD 2014; Walters 1995). A recent version of the criteria for clinical diagnostic lists four essential features (Allen 2003):

1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs (sometimes the urge to move is present without the uncomfortable sensations, and sometimes the arms or other body parts are involved in addition to the legs);
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying or sitting;
3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues;
4. The urge to move or unpleasant sensations are worse in the evening or night than during the day, or only occur in the evening or night (when symptoms are very severe, the worsening at night may not be noticeable but must have been previously present).

Some of the trials identified included patients with Periodic Limb Movement Disorder (PLMD), which is commonly associated with RLS. Studies exclusively examining patients with PLMD (without symptoms of restless legs) were excluded.

Exclusion criteria

We excluded studies that included patients with secondary forms of RLS, such as metabolic, neuropathic, or renal disease.

Types of interventions

We included trials that compared opioid drugs to placebo, to no treatment, or to other drug treatments.

Types of outcome measures

Primary outcomes

Improvement of restless legs symptoms, as assessed by a validated scale (Allen 2001; IRLSSG 2003).

Secondary outcomes

1. Subjective sleep quality (any description about sleep quality, i.e., well-being, improvement of fatigue);
2. Sleep quality, as measured by overnight polysomnography (sleep efficiency, total sleep time, arousal index, PLMS index);
3. Quality of life, as measured by a validated scale, such as the SF-36;
4. Adverse events, described in terms of:
   a. Number of withdrawals due to adverse events;
   b. Number of patients with any adverse events associated with interventions.

Search methods for identification of studies

Electronic searches

1. Cochrane Central Register of Controlled Trials, (CENTRAL) 2016, Issue 4, in *The Cochrane Library* (accessed April 2016; Appendix 1).
2. MEDLINE (1966 to April 2016), using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of randomised controlled trials ;(Appendix 2).
3. EMBASE (1980 to April 2016), using a search strategy adapted from one developed for the Cochrane Collaboration for the identification of randomised controlled clinical trials (Appendix 3).
4. LILACS (1982 to April 2016), using a search strategy adapted from one developed for the Cochrane Collaboration for the identification of randomised controlled clinical trials (Appendix 4).

Searching other resources

We assessed references from original papers and abstracts, reviews, systematic reviews, and meta-analysis to identify any additional studies.
We contacted authors of the included studies to ask if they knew of any relevant unpublished material.

Data collection and analysis

Selection of studies

The search strategies described above were used to obtain titles and abstracts of relevant studies, which were independently screened by LC and KC. They initially retained review articles that might include relevant data or information on trials. The review authors independently assessed the retrieved abstracts, and if necessary, the full text of these studies to determine which studies met the inclusion criteria.

Data extraction and management

The same review authors independently extracted data, using standard data extraction forms. The two review authors entered the data into Review Manager software once all disagreements had been addressed. They had studies reported in non-English language journals translated before being assessed. Where more than one publication of a trial existed, the papers were grouped, and for each available outcome, results were extracted from the publication with the most complete data. We requested further information from the original author by written correspondence as required, and any relevant information obtained in this manner

was included in the review. We resolved all disagreements by consensus, with a third review author if needed.

Assessment of risk of bias in included studies

The same two review authors independently assessed the risk of bias of the included studies, without blinding to authorship or journal. They resolved any disagreement by discussion.

We incorporated the 'risk of bias' assessments into the 'risk of bias' tables, as described in the Cochrane Hankbook for Systematic Reviews of Interventions (Higgins 2011). We considered these criteria: adequate sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessment, incomplete outcome data, selective outcome reporting, and other biases. We assigned 'low risk', 'high risk', or 'unclear risk' judgements to each criterion. 'Unclear risk' indicated there was insufficient information to permit a clear judgement.

We used the GRADE approach to assess quality of the evidence for each outcome across trials, and presented the results in a 'Summary of findings' table. We categorised the primary outcomes at the highest level, and downgraded them due to the following study limitations (risk of bias): limitations in design, inconsistency of results, indirectness of evidence, imprecision of results, and publication bias. We decreased the quality of the evidence by one point if there were serious problems with the risk of bias criteria, or two points if there were very serious problems.

For the 'Summary of findings' table, we analysed the primary outcome: RLS Symptoms, using the International RLS Severity Scale (IRLSSS) and the Clinical Global Impression severity

scale (CGI); drug responders, using the IRLSSS and CGI, and Remitters (decreased symptoms), using the IRLSSS; and the secondary outcomes: adverse events and quality of life (Summary of findings table 1).

Measures of treatment effect

We entered and analysed data in Review Manager 5.3 (RevMan 2014) software. We constructed the 'Summary of findings' tables using the GRADE profiler 3.2.2 software (GRADEpro 2014). For dichotomous variables, risk ratios (RR) with 95% confidence intervals (95% CI) were calculated using the fixed-effects model. Mean differences (MD) with 95% confidence intervals were calculated for continuous outcome variables, using the fixed-effects model.

Unit of analysis issues

Only one trial was included, in a simple parallel group design. In future updates, we may include cross-over trials, only if they allow pooling of data and analysis according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will evaluate the two cross-over periods with a paired analysis, and the carry-over effect

Dealing with missing data

In suspected cases of missing data, we contacted the primary investigator of the study.

Assessment of heterogeneity

As only one study was included, we did not assess heterogeneity. In future updates, we will assess heterogeneity (with the Chi^2 test), which we will assume to be present when the significance level is lower than 0.10 ($P < 0.10$). When significant heterogeneity is present, we will attempt to explain the differences based on clinical characteristics of the included studies.

Assessment of reporting biases

To reduce reporting bias, we contacted as many authors who are involved in RLS research as possible, and asked about any unpublished trials of which they might be aware. We also search the International Committee of Medical Journal Editors for trials that were registered and not published. We had planned to use a funnel plot (trial effect versus trial size) to explore the possibility of publication bias, but did not found sufficient studies (10 or more) for any of the primary analyses.

Data synthesis

As there was only one trial, we did not pool the data with a meta-analysis. In futures updates, for clinically homogeneous studies, we will pool outcomes in meta-analyses, using the fixed-effect model as a default, and the inverse variance method.

Subgroup analysis and investigation of heterogeneity

We did not performed subgroup analysis in this review. In future updates, if a sufficient number of studies (more than 10) are eligible, we will perform subgroup analyses according to age, gender, and duration of treatment. We will categorize periods of treatment as short-term (up to four weeks), or long-term (more than four weeks).

Sensitivity analysis

We did not perform sensitivity analyses, as only one trial was included. Assuming we have sufficient trials in future updates, we will perform sensitivity analyses by omitting trials that include participants with different clinical characteristics, or trials with higher risk of bias.The following strategies will be used for the sensitivity analyses:

1. Separating RCTs published as abstracts.
2. Separating RCTs of lower risk of bias as assessed by allocation concealment.
3. Separating RCTs without an intention-to-treat analysis.
4. Separating cross-over studies from the analysis.

RESULTS

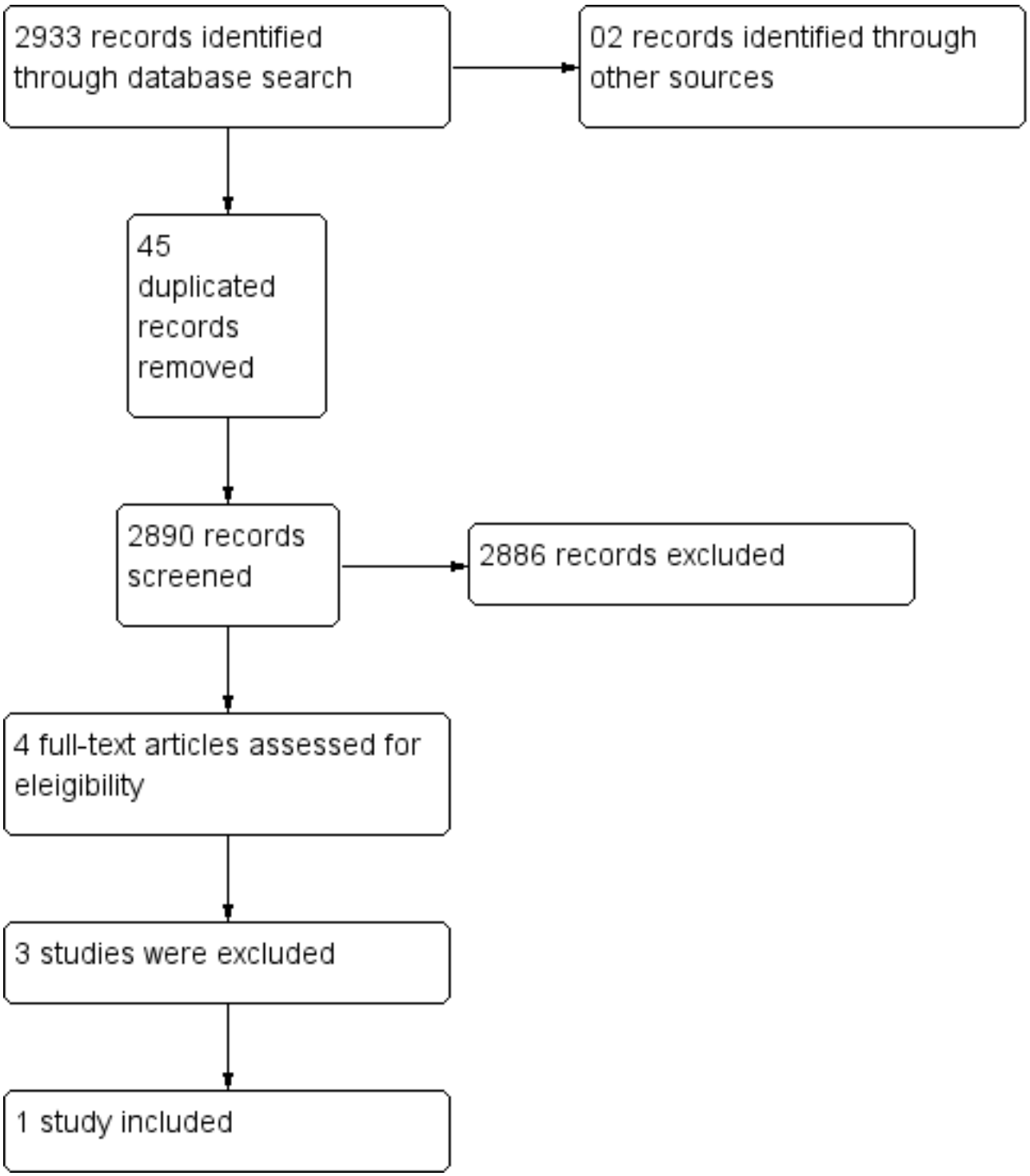
Description of studies

Results of the search

Our search of electronics databases yielded a total of 2935 publications with 45 duplicate records: 246 records from CENTRAL, 2204 from MEDLINE, 483 from EMBASE, none from LILACS, and two from manual sources (Figure 1).. After analysing the title and abstracts, four of these publications were selected for full-text analysis; their eligibility was subsequently confirmed. One study was published first as an abstract in 1991, but we retained only the complete publication for analysis (Kaplan 1993). Allen 1992, Kaplan 1993 and Walters 1993 were excluded because there were insufficient individual cross-over data available to analyse the

variance of the two periods, the wash-out period, or the first period.
We ultimately included one study(Trenkwalder 2013).

Figure 1. Diagram about search, excluded and included researches.



Included studies

Trenkwalder 2013 was a randomised, double-blind, parallel, multicentre trial that enrolled 304 adults with RLS. The patients were recruited from 55 sites in Austria, Germany, Spain, and Sweden. They received progressive doses of prolonged-release oxycodone (maximum 40 mg taken twice daily) and naloxone (maximum 20 mg taken twice daily), or placebo. The investigators used the IRLSSS to assess RLS symptoms, responders and remitters, and the Clinical Global Impression (CGI) scales to assess RLS symptoms, adverse events, and proportion of responders.

Subjective sleep change was measured with the Medical Outcome Study (MOS). Change in disease-specific quality of life was assessed with the RLS-QoL questionnaire. Authors considered responders those patients that scored 50% less in the IRLSSS and those who declared themselves "much improved" or "very much improved" in the CGI scale; remitters those patients that scored 10 or less in the IRLSSS at the end of treatment; reduced symptoms those patients that scored any value less compared to the baseline score.

One hundred patients dropped out of the study due to adverse events, lack of therapeutic effect, patient choice, or administrative reasons. Analysis was completed on a sample of 276 participants according to the intention-to-treat principle, which included all participants who had received at least one dose of the medication or placebo, and for whom follow-up data were available. The included patients had a high mean IRLSSS at baseline (31.6 ± 4.7). We contacted the first author (Dr Claudia Trenkwalder) on 8 November 2013 to ask her how she dealt with the missing data.

Excluded studies

Allen 1992: a randomised, double-blind, cross-over trial of six adult patients. The patients had PLMS and were all diagnosed with RLS on retrospective review. The patients were recruited from The Johns Hopkins Sleep Center, Baltimore, MD, USA. They received progressive doses of propoxyphene (maximum 300 mg), carbidopa/levodopa (maximum 100mg/200mg), or placebo for two weeks prior to polysomnographic studies. We contacted the first author (Dr. Richard Allen) on 20 October 2013, who provided some important information, but the available data were not sufficient or sufficiently detailed to enable inclusion of the study in this review.

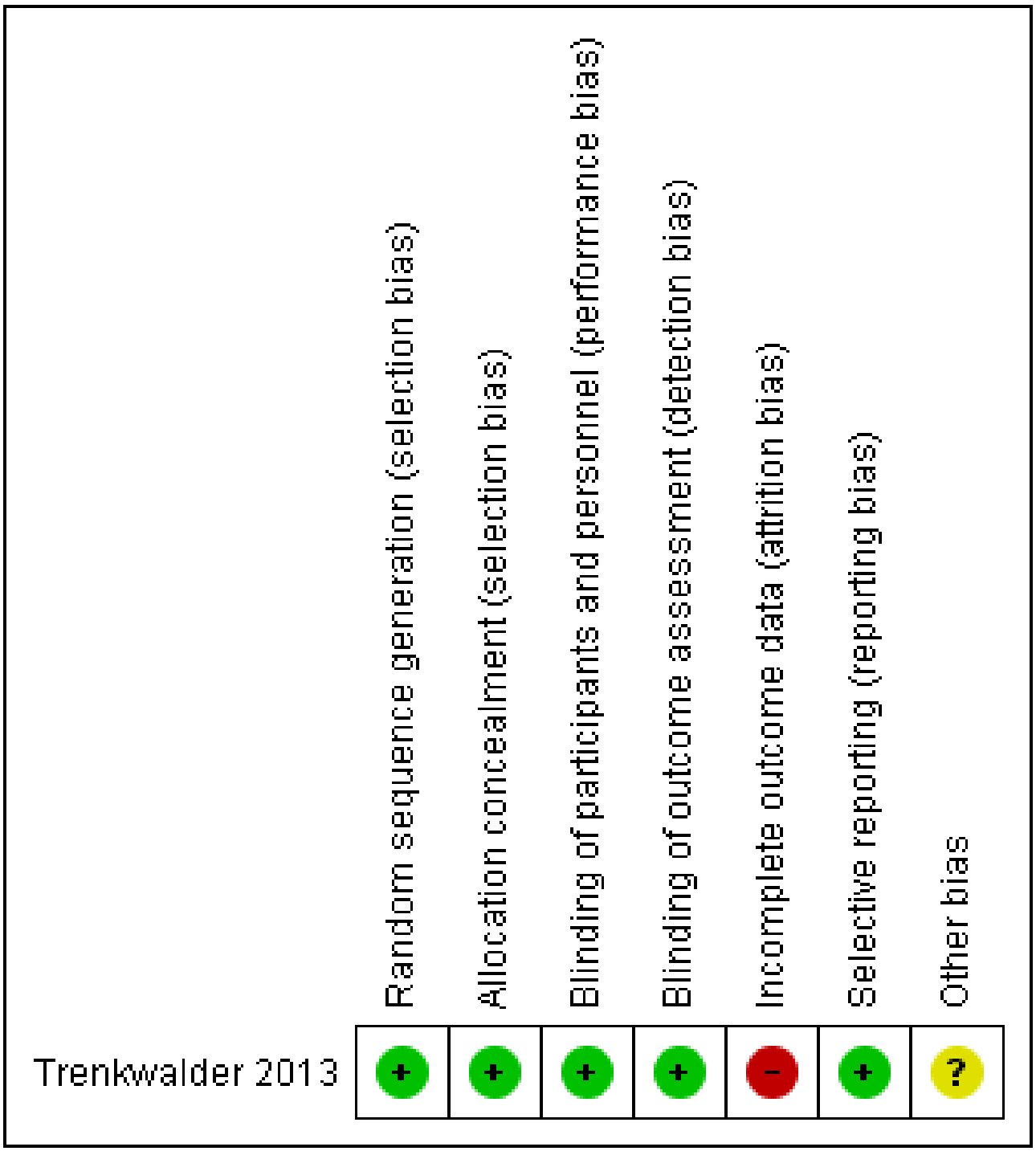
Kaplan 1993: a randomised, double-blind, cross-over trial of six adult patients with PLMS who were all diagnosed with RLS on retrospective review. This new sample of patients was recruited from The Johns Hopkins Sleep Center, Baltimore, MD, USA. They received progressive doses of propoxyphene (maximum 200 mg), carbidopa/levodopa (maximum 100 mg/200 mg), or placebo for two weeks prior to polysomnographic studies. We contacted one of the authors (Dr. Richard Allen) on 20 October 2013, who provided some important information, but the available data were not sufficient or sufficiently detailed to enable inclusion of the study in this review.

Walters 1993: a randomised, double-blind, cross-over trial of 11 adult patients with RLS and PLMS. The diagnosis of RLS was established clinically by the presence of: abnormal sensations, primarily in the legs, motor restlessness, and worsening of paraesthesias and motor restlessness at night and at rest. The patients were recruited from the Lyons VA Medical Center, UMDNJ-Robert Wood Johnson University Hospital, and the Sleep Disorders Center of Columbia Presbyterian Medical Center. They received progressive doses of oxycodone or placebo under guidance of a member of the research group, to relieve symptoms. Oxycodone or placebo capsules were tapered off in three days, and the second-phase dose titration started immediately. Paresthesias, motor restlessness, and daytime alertness were rated on a symptom severity scale of zero to four, for two weeks prior to polysomnographic studies, and on the night of polysomnography. We contacted the first author (Dr Arthur Walters) on 16 October 2013, who provided some important information, but again, the available data were not sufficient or sufficiently detailed to enable inclusion of the study in this review.

Risk of bias in included studies

The 'Risk of bias' assessments for the included study can be found in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias criterion for each included study.



Allocation

Low risk: the randomisation was conducted with a validated interactive response technology system that automated the random assignment of treatment groups to randomisation numbers by site, in blocks of four.

Blinding

Low risk for performance bias: matching placebo tablets (identical in appearance, colour, and taste).

Low risk for detection bias: during the double-blind phase, patients and all personnel involved in the conduct and interpretation of the study (including investigators, site personnel, and sponsor staff) were masked to treatment assignment.

Incomplete outcome data

High risk: a total of 306 patients was randomised, but only 174 completed the 12 week study; intention-to-treat analysis was provided.

Selective reporting

Low risk: all relevant clinical outcomes were analysed; no subgroup analysis was performed; supplementary data was also available.

Other potential sources of bias

Unclear risk: study was proposed by Mundipharma; the principle investigator and three investigators declared conflict of interest with this pharmaceutical company.

Effects of interventions

See: **Summary of findings for the main comparison** Opioids compared to placebo for RLS

Primary outcome measure

RLS Symptoms

In the Trenkwalder 2013 study (N = 276), RLS symptoms, measured on the IRLSSS were reduced more in the opioids group than in the placebo group (MD -7.0; 95% CI -9.69 to -4.31; Analysis 1.1; Figure 3). Symtoms measured on the scale also improved more in the opioid group than in the placebo group (MD -1.11; 95% CI -1.49 to -0.73; Analysis 1.2;).The proportion of drug responders measured on the IRLSSS was greater in the opioid group than in the placebo group (RR 1.82; 95% CI 1.37 to 2.42; Analysis 1.3; Figure 4). Measured on the CGI scale, the proportion of participants who responded in the opioid group was higher than in the placebo group (RR 1.92; 95% CI 1.49 to 2.48; Analysis 1.4;).The proportion of remitters, measured by the IRLSSS was greater in the opioid group than in the placebo group (RR 2.14; 95% CI 1.45 to 3.16; Analysis 1.5; Figure 5). The quality for these three outcomes was downgraded to low because of attrition bias (Summary of findings for the main comparison).

Figure 3. Forest plot of comparison: 1 opioids and placebo, outcome: 1.1 RLS symptoms - IRLSSS.

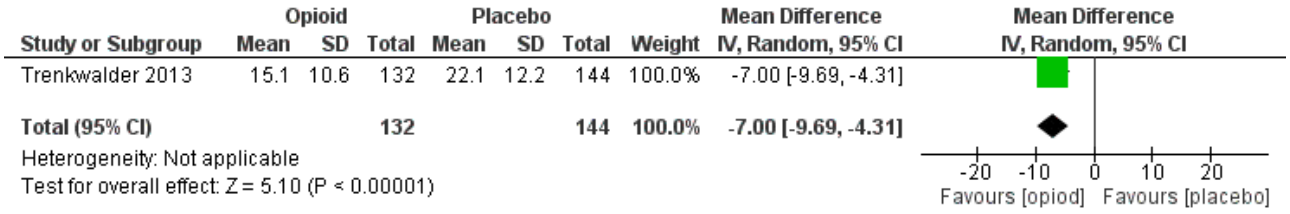


Figure 4. Forest plot of comparison: 1 opioids and placebo, outcome: 1.3 Drug responders - IRLSSS.

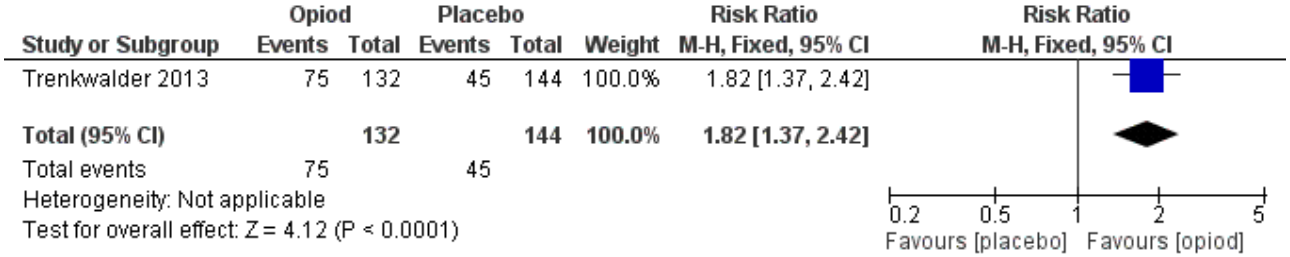


Figure 5. Forest plot of comparison: 1 opioids and placebo, outcome: 1.5 Remitters - IRLSSS.

Secondary outcome measures

Quality of Sleep

Quality of sleep was improved in the drug group more than in the placebo group, measured by sleep adequacy (MD -0.74; 95% CI -1.15 to -0.33; Analysis 1.6); and sleep quantity (MD 0.89; 95% CI 0.52 to 1.26; Analysis 1.7). There was no significant difference between groups for daytime somnolence (MD 0,21; 95% CI -0.13 to 0.55; Analysis 1.8), trouble staying awake during the day (MD 0,13; 95%

CI -0.19 to 0.45; Analysis 1.9), or naps during the day (MD 0,01; 95% CI -0.32 to 0.34; Analysis 1.10).

Quality of LIfe

Quality of life improved more in the opioid group than in the placebo group (MD -0.73; 95% CI -1.10 to -0.36; Analysis 1.11;). The quality of evidence for this outcome was downgraded from to low because of attrition bias (Summary of findings for the main comparison).

Adverse Events

Trenkwalder 2013 (N = 304) reported more adverse events (gastrointestinal problems, fatigue, and headache) in the opioid group than in the placebo group (RR 1.22; 95% CI 1.07 to 1.39; Analysis 1.12; Figure 6). Thirty patients (9.8%) left the study for drug-related adverse events. The quality of the evidence for this outcome was downgraded to low because of attrition bias (Summary of findings for the main comparison).

Figure 6. Forest plot of comparison: 1 opioids and placebo, outcome: 1.12 Adverse Events.

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DISCUSSION

Summary of main results

In the Trenkwalder 2013 study, patients in the oxycodone group showed improvements in RLS symptom and quality of life at week 12. Adverse events were significantly more common in the oxycodone group. The symptoms score mean difference was seven points less (CI: -9.69 to -4.31) in the IRLSSS, and one point less (CI: -1.49 to -0.73) in the CGI in the opioid group after 12 weeks of treatment. Although the quality of life improved only marginally, this finding could be related to the observational period, which may have been too short to provide an accurate perception of that impact. All patients in the opioid group reduced symptoms and improved quality of life and quality of sleep.

Despite the large number of participants who did not complete the planned 12 weeks of treatment, this study provided essential information about the use of opioids to relieve RLS symptoms. Although only 174 patients completed the planned 12 weeks of treatment (100 patients, or 33%, discontinued), analysis was done according to the intention-to-treat principle, and all participants who took at least one dose of medication (or placebo) and provide data during the first week of follow-up were analysed. It is important to state that the reduction of RLS symptoms was significant as early as the first week of treatment, suggesting that this intervention could relieve patients' symptoms quickly. The number of drug responders in the oxycodone/naloxone group was greater than in the placebo group, and there were twice as many drug remitters (patients who became symptoms-free) in the oxycodone/naloxone group than in the placebo group, resulting in a low effect of the intervention. The adverse events reported by Trenkwalder 2013 low the effect of the intervention, which is an important contribution to our understanding of the impact of opioid treatment on patients. Opioids are classically used to treat pain, and the most important concern about their use is the potential for abuse and dependency, although it might not be an issue for RLS patients (Aurora 2012; Silver 2011; Walters 2001). Opioids are associated with constipation, and have the potential to worsen or trigger central sleep apnoea (Randerath 2012). In this regard, it should be noted that only one patient had withdrawal symptoms after 12 weeks in the Trenkwalder 2013 study.

Overall completeness and applicability of evidence

This review included only one study (Trenkwalder 2013; N = 304), in which patients for whom previous treatment had failed were given oxycodone/naloxone twice daily at a mean dose of 20 mg oxycodone and 10 mg naloxone. The intervention was effective in relieving symptoms and improving quality of life, which are the most important outcomes when treating patients with RLS, measured according to the Clinical Global Impression scale and RLS Quality of Life questionnaire (RLS-QoL). Although patients reduced RLS symptoms score at the end of the treatment compared to the placebo group, the authors did not report the minimum clinically important change to be expected for the IRLSSS. Trenkwalder 2013 did not address polysomnographic variables such as total sleep time or periodic leg movement in sleep. The authors carefully screened patients, excluding those with secondary RLS, those taking dopamine receptor blockers, those with co-morbidities (apnoea syndrome, narcolepsy, myoclonus epilepsy, hallucinations or psychotic episodes, acute clinical augmentation, clinically evident respiratory disorders, clinically relevant constipation, or ileus), previous treatment with naloxone or naltrexone within 30 days of entry, contraindications or hypersensitivity to oxycodone, naloxone, related products, or other ingredients, drugs that potentially affected sleep architecture or motor manifestations during sleep, CNS depressants, current alcohol or drug misuse (including opioids), taking an investigational drug within 30 days of study entry, or taking monoamine oxidase inhibitors within two weeks of screening. Shift workers and patients with serum ferritin below 30 µg/L at screening were also excluded. Pregnant women were also not included, although this was not stated in the published text. All these restriction reflect the current caution towards the use of opioids to treat RLS symptoms, mostly derived from the medical experience of using opioids in the treatment of pain-related syndromes. On the other hand, physicians should bear

in mind that the external validity of oxycodone/naloxone treatment for RLS could be an issue in this review.

Quality of the evidence

The conclusions of this review are based on a single study of low evidence quality (Summary of findings for the main comparison, Trenkwalder 2013), which was well-designed and performed overall. This study was downgraded to a low evidence quality because of high attrition bias. As stated above, this study had a large number of dropouts before the planned 12 weeks of treatment, and thus may have underestimated the occurrence of adverse events (attrition bias), including potentially serious adverse events; this, however, may have been minimized by the use of intention-to-treat analysis (ITT). External validity is also an issue in this review, since the included study addressed patients with moderate or severe RLS in whom previous treatment had failed. Although the ITT analysis favours their conclusions about the benefits of the intervention, the high attrition bias precludes prediction of the entire range of possible adverse events for the oxycodone/naloxone treatment, which is an important issue when we are using opioids.

Potential biases in the review process

It is always possible that some clinical trials were performed and not published, published locally (e.g., as theses or dissertations), or in languages not included in the search strategy. Another potential source of bias was that we could not include three cross-over studies, since the primary data required for standard analysis were not available (Allen 1992; Kaplan 1993; Walters 1993).

Agreements and disagreements with other studies or reviews

This systematic review suggests that opioids seem to be effective in the treatment of RLS. This finding is supported by one, multicentre trial (Trenkwalder 2013; N = 304), confirming what has been suggested by previous small, randomised, double-blind, cross-over studies (Allen 1992; Kaplan 1993; Walters 1993). Compared to this study, other available systematic reviews do not add further information, since they were based on those three small trials that we excluded from this review for methodological reasons (Hornyak 2014; Wilt 2012; Wilt 2013.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review found low evidence, based on one trial, in favour of prolonged release oxycodone/naloxone to treat RLS symptoms in patients who had failed previous treatment. The benefits of opioids included amelioration of subjective RLS symptoms and improved quality of life. Adverse events were common during opioid treatment. They were mostly mild to moderate in severity and included gastrointestinal complaints (obstipation, ileus, sub-ileus, nausea, vomiting, flank pain), fatigue, headache, somnolence, dizziness, dry mouth, and pruritus. Withdrawal symptoms were also reported.

Further large, well-designed, randomised clinical trials, that address issues such as minimal clinically important change in RSL symptoms, adverse events, and respiratory polysomnographic data, are still required before clinicians should consider prescribing opioids to treat symptoms of RLS.

Implications for research

Many opioid drugs are available to use in RLS, and it would be of interest to perform randomised clinical trial to assess the effect of these agents in this very distressing condition. Even though opioids have demonstrated effectiveness for the treatment of RLS symptoms, this drug class still has to be compared to other agents recommended for RLS. Furthermore, the impact of opioid treatment on sleep variables as assessed by polysomnography should be evaluated.

ACKNOWLEDGEMENTS

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Trenkwalder 2013

Methods	Randomised controlled trial Analysis: RLS treatment with prolonged release oxycodone/naloxone or placebo Treatment duration: 12 weeks (blinding phase) Follow-up: 40 weeks (open label) Center: Multicentre study conducted at 55 sites in Austria, Germany, Spain, and Sweden
Participants	N = 304 Drop out in the first week = 28 Drop out up to the 12th week = 130 Oxycodone/naloxone group (safety population) = 132 Placebo group (safety population) = 144 Diagnosis: presence of the four classic symptoms of RLS for at least 6 months, failed treatment of symptoms, and no regular intake of opioid-containing drugs at any time before enrolment. Exclusions: secondary RLS or RLS associated with previous or concomitant dopamine receptor blocking drugs, history or presence of sleep apnoea syndrome, narcolepsy, myoclonus epilepsy, hallucinations or psychotic episodes, acute clinical augmentation according to Max Planck Institute diagnostic criteria, treatment with naloxone or naltrexone within 30 days of study entry, and a contraindication or hypersensitivity to oxycodone, naloxone, related products, or other ingredients, evident respiratory disorders, clinically relevant constipation, or ileus, drugs likely to have affected sleep architecture or motor manifestations during sleep or other CNS depressants, current alcohol or drug misuse, history of opioid misuse, taking an investigational drug within 30 days of study entry, serum ferritin less than 30 µg/L at screening, having taken monoamine oxidase inhibitors within 2 weeks of screening. Stable non-opioid analgesic regimens prescribed for reasons other than RLS could be continued during the study. Gender: 202 female, 104 male Race: 99% white in the drug group and 100% white in the placebo group Age: Drug group, mean age 63.1 ± 11.4 years; Placebo Group, mean age 61.7 ± 11.0 years. Setting: 55 hospitals and specialised private neurology practices sites in Austria, Germany, Spain, and Sweden
Interventions	Group 1: oxycodone (N = 132) Group 2: placebo (N = 144) Group 1 treatment schedule: prolonged release oxycodone/naloxone up-titrated during the first 6 weeks to the best dose (maximum oxycodone 40 mg, naloxone 20 mg, twice daily)

Trenkwalder 2013 *(Continued)*

	Group 2 treatment schedule: matching placebo tablets (identical in appearance, colour, and taste).
Outcomes	International Restless Legs Syndrome Severety Scale (IRLSSS,ranging from 0 to 40): change from baseline difference between drug and placebo. Clinical Global Impression (CGI): severity (item 1) and assessment of therapeutic effect (item 3) Resltess Legs Syndrome Quality of Life questionnaire (RLS-QoL): quality of life specific for this disease, 12-point rating scale ranging from 0 to 4. RLS-6 scores: symptom severity at different times during day and night; data not shown RLS leg or arm pain score (numerical, 11-point rating scale ranging from 0 to 10) Proportion of treatment responders and remitters on the IRLSSS and CGI scales Augmentation: patients who reported worsening disease were assessed for augmentation with the Max Planck Institute diagnostic criteria. Adverse events: premature study discontinuation because of adverse events, changes in clinical laboratory parameters, vital signs, 12-lead electrocardiogram, physical examinations, or CGI-4 score
Notes	Funding and other possible conflicts: Mundipharma Research. The sponsor also proposed the idea for this study and took part in all stages of research. According to the authors, the sponsor allowed access to all data, and interpretation of said data and the published text were under their responsibility. The article was prepared by the authors with the support of a medical writer paid for by the sponsor.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation sequences were generated by the sponsor and checked for accuracy by an unmasked statistician who had no other role in the study. Treatment allocations were not made available until the study was completed and after the final clinical database lock, except in the case of an emergency.
Allocation concealment (selection bias)	Low risk	Randomisation with a validated interactive response technology system that automated the random assignment of treatment groups to randomisation numbers by site in blocks of four.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching placebo tablets (identical in appearance, colour, and taste).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	During the double-blind phase, patients and all personnel involved in the conduct and interpretation of the study (including investigators, site personnel, and sponsor staff) were masked to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	High risk	A total of 306 patients was randomised and 174 completed the study; intention-to-treat analysis was provided.
Selective reporting (reporting bias)	Low risk	All relevant clinical outcome were analysed; no subgroup analysis was performed. Supplementary data were also available.
Other bias	Unclear risk	Study was proposed by Mundipharma and the Primary Investigator and more two investigators declared conflict of interest with this pharmaceutical company.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Allen 1992	There was no information about the washout period; the data were not provided for each period; we were unable to analyse the variance or to use the first period data.
Kaplan 1993	There was no information about the washout period; the data were not provided for each period; we were unable to analyse the variance or to use the first period data.
Walters 1993	There was no information about the washout period; the data were not provided for each period; we were unable to analyse the variance or to use the first period data.

DATA AND ANALYSES

Comparison 1. opioids and placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 RLS symptoms - IRLSSS	1	276	Mean Difference (IV, Random, 95% CI)	-7.00 [-9.69, -4.31]
2 RLS symptoms - CGI	1	276	Mean Difference (IV, Fixed, 95% CI)	-1.11 [-1.49, -0.73]
3 Drug responders - IRLSSS	1	276	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [1.37, 2.42]
4 Drug responders - CGI	1	276	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [1.49, 2.48]
5 Remitters - IRLSSS	1	276	Risk Ratio (M-H, Fixed, 95% CI)	2.14 [1.45, 3.16]
6 Sleep adequacy - MOS	1	276	Mean Difference (IV, Fixed, 95% CI)	-0.74 [-1.15, -0.33]
7 Sleep quantity - MOS	1	276	Mean Difference (IV, Fixed, 95% CI)	0.89 [0.52, 1.26]
8 Daytime somnolence - MOS	1	276	Mean Difference (IV, Fixed, 95% CI)	0.21 [-0.13, 0.55]
9 Trouble staying awake during the day - MOS	1	276	Mean Difference (IV, Fixed, 95% CI)	0.13 [-0.19, 0.45]
10 Naps during the day - MOS	1	276	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.32, 0.34]
11 Quality of life - RLS QoL	1	276	Mean Difference (IV, Fixed, 95% CI)	-0.73 [-1.10, -0.36]
12 Adverse Events	1	304	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [1.07, 1.39]

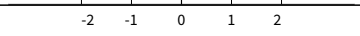
Analysis 1.1. Comparison 1 opioids and placebo, Outcome 1 RLS symptoms - IRLSSS.

Study or subgroup	Opioid N	Opioid Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Trenkwalder 2013	132	15.1 (10.6)	144	22.1 (12.2)		100%	-7[-9.69,-4.31]
Total * **	**132**		**144**			**100%**	**-7[-9.69,-4.31]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.1(P<0.0001)							

Favours [opiod] Favours [placebo]

Analysis 1.2. Comparison 1 opioids and placebo, Outcome 2 RLS symptoms - CGI.

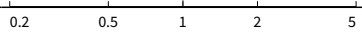
Study or subgroup	Opioid N	Opioid Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Trenkwalder 2013	132	3 (1.5)	144	4.1 (1.7)		100%	-1.11[-1.49,-0.73]
Total * **	**132**		**144**			**100%**	**-1.11[-1.49,-0.73]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.78(P<0.0001)							



Favours [opioid] Favours [placebo]

Analysis 1.3. Comparison 1 opioids and placebo, Outcome 3 Drug responders - IRLSSS.

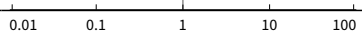
Study or subgroup	Opiod n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Trenkwalder 2013	75/132	45/144		100%	1.82[1.37,2.42]
Total (95% CI)	**132**	**144**		**100%**	**1.82[1.37,2.42]**
Total events: 75 (Opiod), 45 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=4.12(P<0.0001)					



Favours [placebo] Favours [opiod]

Analysis 1.4. Comparison 1 opioids and placebo, Outcome 4 Drug responders - CGI.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Trenkwalder 2013	88/132	50/144		100%	1.92[1.49,2.48]
Total (95% CI)	**132**	**144**		**100%**	**1.92[1.49,2.48]**
Total events: 88 (Experimental), 50 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=5.03(P<0.0001)					



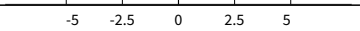
Favours [placebo] Favours [opioid]

Analysis 1.5. Comparison 1 opioids and placebo, Outcome 5 Remitters - IRLSSS.

Study or subgroup	opiod n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Trenkwalder 2013	55/132	28/144		100%	2.14[1.45,3.16]
Total (95% CI)	**132**	**144**		**100%**	**2.14[1.45,3.16]**
Total events: 55 (opiod), 28 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.84(P=0)					

Analysis 1.6. Comparison 1 opioids and placebo, Outcome 6 Sleep adequacy - MOS.

Study or subgroup	Opioid N	Opioid Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Trenkwalder 2013	132	3.3 (1.7)	144	4 (1.7)		100%	-0.74[-1.15,-0.33]
Total ***	**132**		**144**			**100%**	**-0.74[-1.15,-0.33]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.54(P=0)							



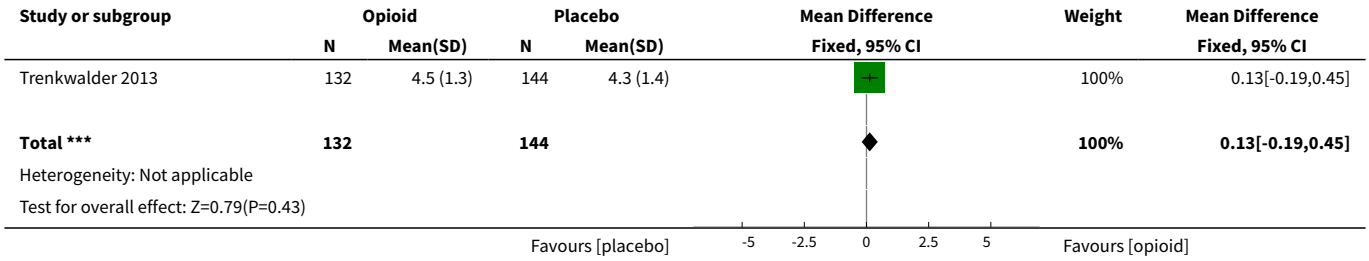
Analysis 1.7. Comparison 1 opioids and placebo, Outcome 7 Sleep quantity - MOS.

Study or subgroup	Opioid N	Opioid Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Trenkwalder 2013	132	6.3 (1.3)	144	5.4 (1.8)		100%	0.89[0.52,1.26]
Total ***	**132**		**144**			**100%**	**0.89[0.52,1.26]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.76(P<0.0001)							

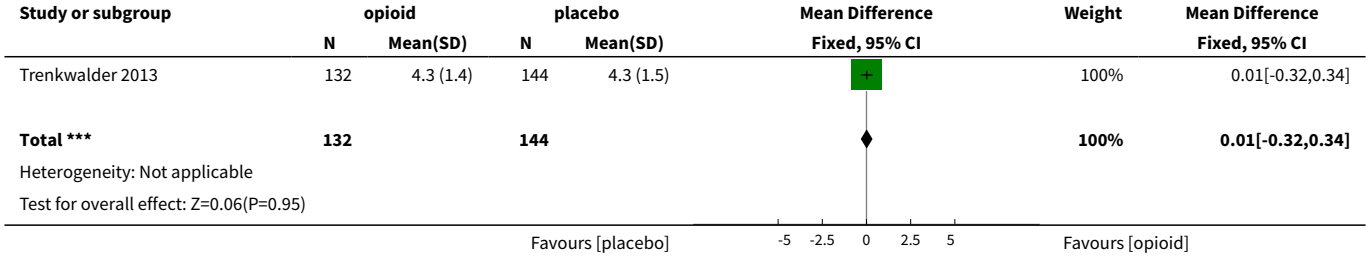
Analysis 1.8. Comparison 1 opioids and placebo, Outcome 8 Daytime somnolence - MOS.

Study or subgroup	opioid N	opioid Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Trenkwalder 2013	132	3.7 (1.4)	144	3.5 (1.5)		100%	0.21[-0.13,0.55]
Total ***	**132**		**144**			**100%**	**0.21[-0.13,0.55]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.22(P=0.22)							

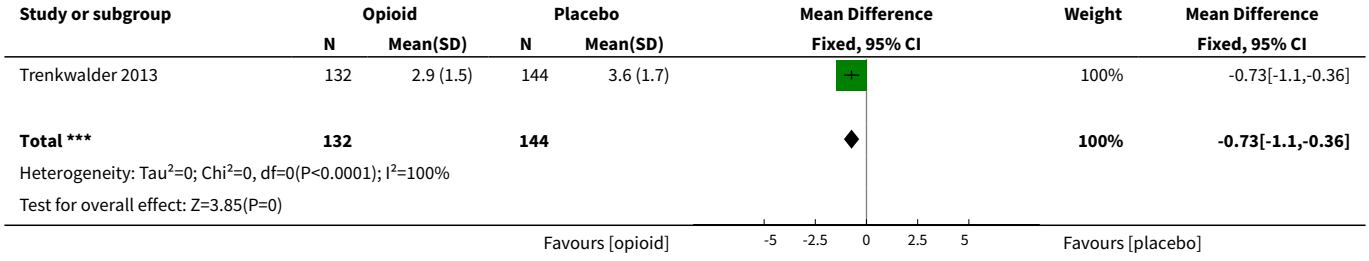
Analysis 1.9. Comparison 1 opioids and placebo, Outcome 9 Trouble staying awake during the day - MOS.



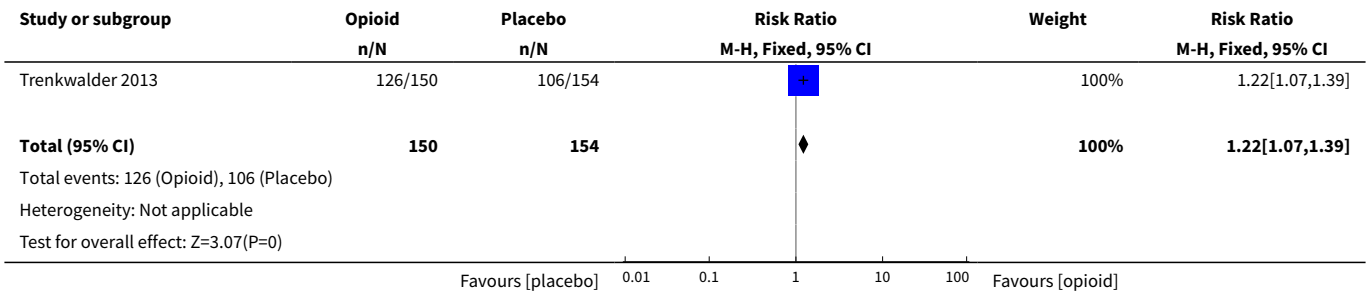
Analysis 1.10. Comparison 1 opioids and placebo, Outcome 10 Naps during the day - MOS.



Analysis 1.11. Comparison 1 opioids and placebo, Outcome 11 Quality of life - RLS QoL.



Analysis 1.12. Comparison 1 opioids and placebo, Outcome 12 Adverse Events.



APPENDICES

Appendix 1. CENTRAL search strategy

"#1 RESTLESS LEGS SYNDROME
"#2 (restless next leg*)
"#3 (ekbom* next syndrome)
"#4 (periodic next leg next movements*)
"#5 (periodic next limb next movements*)
"#6 (PLM or PLMS or PLMD)
"#7 (#1 or #2 or #3 or #4 or #5 or #6)

Appendix 2. MEDLINE search strategy

"MEDLINE search strategy (1966 to most recent):
"#1 restless legs syndrome [Text Word]
"#2 restless legs syndrome [All Fields]
"#3 ekbom syndrome [All Fields]
"#4 (periodic [All Fields] OR movement [All Fields]) AND (leg OR legs)
"#5 (periodic [All Fields] OR movement [All Fields]) AND (limb OR limbs)
"#6 (periodic [All Fields] OR movement [All Fields]) AND extremities [All Fields]
"#7 nocturnal myoclonus syndrome [All Fields]
"#8 periodic limb movement disorder
"#9 periodic limb movement disorders
"#10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
"#11 "morphine" [All Fields]
"#12 "hydromorphone" [All Fields]
"#13 "levorphanol" [All Fields]
"#14 "meperidine" [All Fields]
"#15 "methadone" [All Fields]
"#16 "propoxyphene" [All Fields]
"#17 "codeine" [All Fields]
"#18 "pentazocine" [All Fields]
"#19 "hydrocodone" [All Fields]
"#20 "oxycodone" [All Fields]
"#21 "fentanyl" [All Fields]
"#22 "tramadol" [All Fields]
"#23 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
"#24 #10 AND #23

Appendix 3. EMBASE search strategy

"EMBASE search strategy (1980 to most recent):
"#1 Restless Legs Syndrome/
"#2 restless leg$.tw
"#3 Ekbom$ syndrome.tw
"#4 periodic leg movement$.tw
"#5 periodic limb movement$.tw
"#6 (PLM or PLMS or PLMD).tw
"#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
"#8 "morphine" .tw
"#9 "hydromorphone" .tw
"#10 "levorphanol" .tw
"#11 "meperidine" .tw
"#12 "methadone" .tw
"#13 "propoxyphene" .tw
"#14 "codeine" .tw
"#15 "pentazocine" .tw
"#16 "hydrocodone" .tw
"#17 "oxycodone" .tw
"#18 "fentanyl" .tw
"#19 "tramadol" .tw
"#20 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19

"#21 #7 AND #20

Appendix 4. LILACS search strategy

"LILACS search strategy (1982 to most recent):
"#1 síndrome das pernas inquietas [Palavras]".
"#2 (tw syndrome or tw sindrome) and (leg or legs or pierna$ or perna$ or limb$) [Palavras] and inquieta$ or restless
"#3 (movement$ and periodic) [Palavras]
"#4 #1 OR #2 OR #3
"#5 "morphine" [Palavras]
"#6 "hydromorphone" [Palavras]
"#7 "levorphanol" [Palavras]
"#8 "meperidine" [Palavras]
"#9 "methadone" [Palavras]
"#10 "propoxyphene" [Palavras]
"#11 "codeine" [Palavras]
"#12 "pentazocine" [Palavras]
"#13 "hydrocodone" [Palavras]
"#14 "oxycodone" [Palavras]
"#15 "fentanyl" [Palavras]
"#16 "tramadol" [Palavras]
"#17 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
"#18 #4 AND #17

F E E D B A C K

GRADE assessment, 30 June 2016

Summary

Date of Submission: 30-Jun-2016

Name: Andrew Moore

Email Address: andrew.moore@ndcn.ox.ac.uk

Affiliation: University of Oxford

Role: Author and editor

Comment:

First of all, it is really nice to see a review on restless legs. Typically for RLS there are few studies, and this review included only a single study.

I have no real issue with the way the review was done, but I am concerned that the GRADE assessment of moderate quality evidence may overstate how much reliance we can put on the evidence. My concerns are twofold, and both of them are based on solid evidence which does not yet form part of Cochrane guidance.

The first is the issue of imputation. In chronic pain it is becoming increasingly clear that any benefits of opioids derives from the use of last observation carried forward in a situation of high dropout rates (30-60%, often early). LOCF means that someone might benefit at 2 weeks, but cannot take the tablets and so drops out. The beneficial result at week 2 is then treated as if it occurred at week 12. But if the patient cannot take the tablet, then they can't get benefit. In terms of the patient, the treatment has failed, but the imputation method treats it as a success. In chronic pain, even in studies examined by the FDA, LOCF overstates treatment effect to a very large degree - so that as yet no opioid has been shown to be effective if an outcome of useful pain relief AND taking the tablets at 12 weeks is used. The results show either no difference between opioid and placebo, or even statistically worse than placebo. There are analyses of the use of imputation methods showing that situations where LOCF is used are problematical when adverse event withdrawals are higher with active than placebo, as in the trial in this review. In the USA there have been major reports recently highlighting concern at use of LOCF.

I have read the paper several times, and I am not cure how data were handled to achieve an IRLSSG response of 50% reduction, or PGIC of much or very much improved. Thought these figures imply NNTs of about 4 and 3 respectively - useful degree of benefit - it might have been much less useful if all withdrawals were considered treatment failure. Unless one knows that, then moderate quality overstates the case.

Probably less important but also relevant is the question of study size. Small size is also known to be associated with overestimation of treatment effects, as well as issues of random chance affecting estimation of magnitude of effect. At the sizes in the single trial, then the latter at least might apply, though the study itself was impeccably conducted. Another reason to be cautious about how good the result is. I can provide references for all this if needed.

GRADE is useful as long as the GRADE of evidence is appropriate, and how much value there is in having three levels that basically say that we don't know that the results are much good. On balance I would suggest that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate - Low quality.

But thanks again for demonstrating just how little evidence there is in this important condition. It is very much the same as chronic pain.

Reply

We are very much thankful to Dr. Moore for the time spent analyzing our Cochrane Systematic Review on Opioids for restless legs syndrome (RLS) treatment. We agree with the comments and arguments about the last observation carried forward (LOCF). Including observations from patients that dropped out early in the study could bring a real bias to the results. The LOCF implies in an imputation, which could not be of value to patients suffering from a chronic condition like RLS. The drug bears a potential benefit, but could not be of value in the real-world, which means that at the end of the protocol it would be similar or worse than the placebo. To avoid the early drop out problem influencing negatively the results, we should apply the concept of the worst scenario, i.e., early dropout must be considered as treatment failing. This was not done in the single studied included.

Although the primary study was rigorously conducted, and many centers collaborated, the number of patients included in the trial was small when we aim to demonstrate unequivocal evidence.

Taking into account all the issues raised above, we agreed in downgrading the level of the evidence to low. We have already incorporated this change in the RevMan.

We appreciate the opportunity to address this issue in our review.

Contributors

Author team.

WHAT'S NEW

Date	Event	Description
6 November 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

César Osório: Literature search, data extraction, drafting of written submissions.

Luciane Bizari Coin de Carvalho: study selection, data extraction, statistical analysis, development of final review.

Karla Carlos: study selection, data extraction, statistical analysis, development of final review.

Cristiane Fiquene Conti : Protocol development, literature search.

Marcio Moyses de Oliveira : Protocol development, literature search.

Lucila Bizari Fernandes do Prado: study selection, data extraction, statistical analysis, development of final review.

Gilmar Fernandes do Prado : Protocol development, literature search, study selection, data extraction, statistical analysis, development of final review.

DECLARATIONS OF INTEREST

None known for all authors.

SOURCES OF SUPPORT

Internal sources

- Escola Paulista de Medicina, Universidade Federal de São Paulo, Brazil.

  Salary

External sources

- CAPES and CNPq, Brazil.

  Government Agencies for research support

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics, Opioid [adverse effects] [*therapeutic use]; Disorders of Excessive Somnolence [chemically induced]; Naloxone [adverse effects] [*therapeutic use]; Oxycodone [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Restless Legs Syndrome [*drug therapy]

MeSH check words

Humans